Core Outcome Set for Cardiac Arrest (COSCA) in adults: An Advisory Statement From the International Liaison Committee on Resuscitation

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[h1]Abstract

Cardiac arrest effectiveness trials have traditionally reported outcomes that focus on survival. A lack of consistency in outcome reporting between trials limits the opportunities to pool results for meta-analysis. The Core Outcome Set for Cardiac Arrest (COSCA) initiative, a partnership between patients, their partners, clinicians, research scientists, and the International Liaison Committee on Resuscitation, sought to develop a consensus core outcome set for cardiac arrest for effectiveness trials. Core outcome sets are primarily intended for large, randomized clinical effectiveness trials (sometimes referred to as *pragmatic trials*, *phase III/IV trials*) rather than for pilot or efficacy studies.

A systematic review of the literature combined with qualitative interviews among cardiac arrest survivors was used to generate a list of potential outcome domains. This list was prioritized through a Delphi process, which involved clinicians, patients, and their relatives/partners. An international advisory panel narrowed these down to 3 core domains by debate leading to consensus. The writing group refined recommendations for when these outcomes should be measured and further characterized relevant measurement tools.

Consensus emerged that a core outcome set for reporting on effectiveness studies of cardiac arrest (COSCA) in adults should include survival, neurologic function, and health-related quality of life. This should be reported as survival status and modified Rankin Scale score at hospital discharge and / or 30 days. Health-related quality of life should be measured by using 1 or more tools from Health Utilities Index version 3, Short-Form 36-Item Health Survey, EuroQol 5D-5L at 90 days and at periodic intervals up to 1 year after cardiac arrest, if resources allow.

[h1]Introduction

Sudden cardiac arrest is one of the leading causes of death in industrialized nations. In the United States, approximately 360 000 cardiac arrests are attended by emergency services each year, with only 10.6% of patients surviving to hospital discharge.[1] Similar statistics apply across Europe and all other industrialized areas worldwide.[2, 3] However, survival rates vary widely both globally[4] and regionally,[5, 6] with 4-fold or more regional variations reported. These low and variable survival rates highlight the importance of research that seeks to improve patient outcomes.

Randomized trials are important tools for evaluating the clinical and cost-effectiveness of interventions for in- and out-of-hospital cardiac arrest. Two broad types of trials have been described—efficacy and effectiveness. Efficacy (sometimes called *explanatory*) trials aim to test whether an intervention works under optimal situations. Effectiveness (sometimes called *pragmatic*) trials are designed to assess how well an intervention works in routine clinical practice.[7] Ordinarily, efficacy trials focus on assessing the impact of an intervention on a short-term outcome that is well-correlated with long-term prognosis. Effectiveness trials seek to provide evidence of the longer-term health impact of an intervention.[8, 9] Evaluated outcomes may include clinical, clinician-reported, and patient-reported outcomes and resource use or economic impact. Clinical trials provide essential evidence of the relative benefit of an intervention for stakeholders as diverse as clinicians, patients, and policy makers. Outcome selection is, therefore, an important aspect of trial design.[9, 10]

Sometimes multiple trials may evaluate the same intervention in different settings. Reconciling disparate trial results can be challenging if each trial evaluated different outcomes at different timepoints. A systematic review of cardiac arrest trials published

between 2000 and 2012 included 61 publications that identified more than 160 different trial outcomes.[11] No single outcome was reported across all trials. The majority of outcomes reflected short-term clinical and clinician-reported outcomes, focusing on pathophysiologic manifestations and process-based measures. While survival was the most commonly reported outcome, 39 different definitions of survival were used. Patient-reported outcomes[12] were rarely reported, although more recent trials have included these outcomes.[13, 14] This suggests that essential evidence of the impact of care from the survivors' perspective is currently missing from clinical trials.

Adopting a consistent approach to outcome reporting for effectiveness trials has the potential to reduce heterogeneity in reporting, improve transparency in outcome selection, reduce reporting bias, and increase information available to pool for meta-analysis. Standardized reporting frameworks have been developed for reporting the findings of observational studies drawn from resuscitation registries.[15, 16] These recommend 23 core data elements and 30 supplementary elements across the 5 domains of system, dispatch, patient, process, and outcome.[17] International guidelines exist for core outcomes to use in effectiveness trials in patients with other conditions.[18] Becker et al considered choices of primary outcomes across a range of resuscitation science studies but concluded that no single primary outcome was appropriate for all studies of cardiac arrest.[19] However, no international guidelines exist to define a focused core outcome set (COS) for use in effectiveness trials in patients with cardiac arrest.

The Core Outcome Measures for Effectiveness Trials (COMET) initiative promotes the development and application of agreed standardized sets of outcomes, known as *core outcome sets*.[20]

A COS is defined as a small, standardized group of outcomes that should be measured and reported, *as a minimum*, in all effectiveness trials for a specific health area.[20, 21] Effectiveness trials should aim to capture the COS as part of their *a priori*–defined primary or secondary outcomes.

The COSCA initiative, in collaboration with the International Liaison Committee on Resuscitation (ILCOR), sought to develop a COS for cardiac arrest effectiveness trials covering both in- and out-of-hospital cardiac arrest. This consensus paper draws on the views and experiences of patients, the public, clinicians, policy makers, researchers, and the international perspectives represented through the ILCOR collaborative network. The process was informed by systematic reviews of the literature, as well as qualitative research involving cardiac arrest survivors. A total of 168 participants used a Delphi process to draft a core cardiac arrest outcome set, and a 2-day meeting was convened to develop consensus recommendations.

[h1]Methods

The available evidence associated with the development of COSs[18, 20] and the websites of key COS development groups (COMET and Outcome Measures in Rheumatoid Arthritis Clinical Trials [OMERACT], later renamed *Outcome Measures in Rheumatology*) informed our approach. The project was registered with the COMET initiative (www.comet-initiative.org/studies/details/284). Ethical approval was obtained from the National Health Service Black Country Research Ethics Committee (13/WM/0464) to enable patients/partners to participate.

Development of a COS involved 2 key steps: development of a core domain set (ie, what to measure) followed by identification of appropriate measurement tools (ie, how to measure).[18, 20] A *core domain set* was defined as referring to the minimum number of health domains (outcomes or aspects of health) that must be assessed. That is, it specifies *what* should be measured. Importantly, this stage was driven by what is important and not how an outcome is assessed. The second stage involved the establishment of a core outcome measurement set, that is, the specific methods of assessment (ie, *how* to measure) for the domains identified in step 1. The selection of measurement tools was informed by an appraisal of measurement quality, relevance, and feasibility.

The OMERACT initiative suggests that a COS should seek to include at least 1 health domain across each of 4 core areas of health (Figure 1): 3 core areas consider the impact of a health condition (ie, survival, life impact, economic impact/resource use), and the fourth core area reflects any pathophysiologic manifestations associated with the condition.[18] Several reviews[11, 22, 23] suggest that these domains are relevant and encompass the large number of outcomes assessed in cardiac arrest trials.

To develop the consensus outcome criteria, a 4-stage approach was used, which consisted of the following steps, which are each explained in detail:

- Stage 1: Generation of an extensive list of potential outcomes across 4 core areas of health
- Stage 2: International Delphi to refine and prioritize a list of potential outcomes
- Stage 3: International expert panel meeting
- Stage 4: Synthesis of findings and recommendations for measurement tools

[h2]Stage 1: Generation of an Extensive List of Potential Outcomes Across 4 Core Areas of Health

This stage was informed by a systematic review of the literature and qualitative interviews with cardiac arrest survivors and their partners. The systematic review focused on the identification of outcomes reported from randomized controlled trials that enrolled adults who had sustained a cardiac arrest.[11] The findings from the systematic review were supplemented by conducting semi-structured interviews with adult cardiac arrest survivors (and, if available, their partners) between 3 and 12 months after discharge from hospital following their cardiac arrest. Interviews were conducted, recorded, and transcribed by using NVivo (QSR International 2012) by L.W. Data were analyzed by using Interpretative Phenomenological Analysis, which seeks to capture the individuals' experience of a phenomenon and how they understand their experiences.[24] Findings from the systematic review and qualitative research were synthesized to produce an extensive list of potential outcomes. These were grouped under the OMERACT core area headings of survival, life impact, resource use/economic, and pathophysiologic manifestations of cardiac arrest for consideration in stage 2.

[h2]Stage 2: International Delphi to Refine and Prioritize List of Potential Outcomes

The list of potential outcomes identified during stage 1 were placed into an online survey tool (SurveyMonkey, Dublin, Ireland). Separate surveys were developed for healthcare professionals and patients/patient advocates. The ILCOR network of 7 regional resuscitation councils was used to solicit the views of healthcare professionals and patient and public advocates. Each ILCOR member (n=27) was asked to invite 6 healthcare professionals and 3 patients to participate in the relevant surveys by email. The outcomes were prioritized in 2 rounds. Questions were structured to allow participants to rate the importance of each

outcome at 5 different time points across the patient journey: during cardiopulmonary resuscitation (CPR), immediately after CPR, during hospitalization, at hospital discharge, and within the first year after the cardiac arrest. In the first round, survey participants were also given the opportunity to suggest additional outcomes they considered important if they were not currently included in the survey. At the end of each round, outcomes rated as *critical importance* by greater than 70% of respondents and rated as *limited importance* by less than 15% of respondents were advanced for additional consideration by the expert panel in stage 3. Similarly, those outcomes rated *of limited importance* by greater than 70% of respondents and *of critical importance* by less than 15% of respondents were discarded. The findings from the first round were summarized and presented for a second round of prioritization. Any new suggestions were included in the second round. The second round of prioritization differed by asking participants to rank outcomes according to importance. Outcomes that received strong support (more than 70% agreement) were also advanced for consideration by the expert panel in stage 3. Outcomes that received moderate support (60%–69% agreement) were also presented to the expert panel in stage 3.

[h2]Stage 3: International Expert Panel Meeting

The aim of the international expert panel was to consider the shortlist of outcomes identified during stage 2 and select a COS comprising 4 to 8 outcomes and make recommendations of measurement tools to capture those outcomes. A 2-day consensus meeting was convened in Prague, Czech Republic, in October 2015. A group of experts uninvolved in previous stages was purposefully selected to capture those involved in clinical research (clinicians, clinical trialists, methodologists), experts in the use of measurement tools for cardiac arrest, healthcare providers involved in treating patients with cardiac arrest (physicians, nurses,

paramedics, allied health professionals), and survivors of cardiac arrests and patient advocates.

Before the meeting, the participants were sent a written summary of the outcome selection process described above. At the start of the meeting, an overview of steps undertaken and findings from stages 1 and 2 were presented. The shortlisted outcomes were presented in a matrix that covered the OMERACT core area headings of survival, life impact, resource use/economic, and pathophysiologic manifestations of cardiac arrest during CPR, immediately after CPR, during hospitalization, at hospital discharge, and within the first year after the cardiac arrest. Initial presentations were followed by semi-structured, small-group discussions that covered the 4 core areas. Each core area was assigned a facilitator who supported 4 rounds of discussions on that topic. Each discussion group included a survivor of cardiac arrest or patient advocate, as well as several researchers and clinicians who participated in small-group discussion across each core area. Each group nominated a recorder. The groups were tasked to consider the importance, relevance, acceptability, and feasibility of the short-listed outcomes as potential core outcomes for cardiac arrest effectiveness trials. The facilitator encouraged all group members to participate in discussions and shared key findings from each group with the next. This enabled consideration of and building upon what other participants discussed, facilitated the identification of issues of agreement and disagreement, and supported a flow of new ideas or key issues between groups. Participants, thereafter, reconvened in a whole-group discussion session: facilitators and group recorders summarized feedback from the group discussion, including areas of agreement and disagreement. The large-group discussion sought to collectively explore agreement and refine issues or concerns raised within each core area. At the end of the first day, expert panel members were invited to reflect on the day’s discussions

and then vote for up to 7 outcomes they felt should be included as core outcomes. Secure electronic votes were submitted by using Turningpoint Software and Responseware keypads (Turning Technologies, Youngstown, Ohio, USA). The second day followed a similar model of large- and small-group discussions designed to allow further discussion and reflection on the optimal outcomes. A second round of voting was used to identify the final list of core outcomes. Proceedings were captured in the form of detailed written records from discussion groups, plenary sessions, and the outcome of voting.

[h2]Stage 4: Synthesis of Findings and Recommendations for Measurement Tools

A writing group was appointed by ILCOR and endorsed by the American Heart Association Manuscript Oversight Committee after review for conflicts of interest. The charge to the group was to draw together and summarize the findings from stages 1 through 3. The group met by teleconference on 8 occasions and face-to-face on 1 occasion.

The writing group reviewed and summarized the findings from stages 1 through 3 presented in this scientific statement. The group undertook further work with the intention of making recommendations on relevant measurement tools for the outcome domains selected in stage 3. This was informed by considering existing measurement tools in cardiac arrest and other relevant diseases or injuries and discussing their quality, acceptability, and feasibility for application in clinical trials. Final recommendations were reached through discussion and consensus among the writing group members.

[h1]Results

[h2]Stage 1: Generation of an Extensive List of Potential Outcomes Across 4 Core Areas (OMERACT Framework)

The systematic review identified 61 randomized trials that reported 164 unique outcomes on 278 occasions.[11] The most frequently reported outcome was survival (85% of trials). This included return of spontaneous circulation (ROSC) before hospital admission, in the emergency department, or at any point during the resuscitation attempt. Survival was reported at various time points from emergency department admission, hospital discharge, and through to 3 years. There was a lack of consistency in definition and the time points at which survival was assessed, although most studies (90%) reported survival up to, and including, hospital discharge. Pathophysiologic outcomes (eg, coronary perfusion pressure, arterial blood gas results) and life impact were frequently reported, although there was a lack of consistency in outcomes, measurement tools, and the timings of assessments. Process of care (eg, event timings), response to treatment (eg, temperature achieved in targeted temperature management trials), quality of CPR, intervention success rates (eg, vascular access) and adverse outcomes were reported in a quarter of studies. Writing group members identified trials published more recently that reported outcomes in the domain of life impact.[13, 14, 25, 26]

Eleven interviews (8 patients, 3 partners) were conducted to provide a detailed understanding of the lived experience of those surviving cardiac arrest. Five key themes were identified by patients reflecting the disruption to normality caused by cardiac arrest (survival, physical activities, emotional well-being, social well-being, and the impact on others; Table 1).

The findings from the systematic review and patient/partner interviews were used to produce an extensive list of 53 potential outcomes, encompassing survival (5), life impact (24), economic impact and resource use (10), and pathophysiologic manifestations (14), which were used in the stage 2 Delphi process.

[h2]Stage 2: International Delphi to Refine and Prioritize Long List of Potential Outcomes

Ninety-nine healthcare professionals, 62 cardiac arrest survivors and 7 relatives of cardiac arrest victims from 15 countries participated in the Delphi survey. The clinician group included: 46 physicians, 12 nurses, 20 allied health professionals and 6 academics. By the end of the 2 Delphi rounds, 25 outcome domains were prioritized (Figure 2).

[h2]Stage 3: International Expert Panel Meeting

A total of 23 expert panel members (including 2 survivors, 1 partner, and 1 patient advocate) participated from 11 countries (UK, the Netherlands, Finland, Germany, Belgium, Sweden, United States, Canada, Singapore, Australia, and New Zealand). The core outcome discussions and recommendations are summarized below.

[h3]Pathophysiologic Manifestations

The expert panel considered circulatory function, respiratory function, and brain function as potential core outcomes. There was general agreement that the assessment of these outcomes is of high importance during and immediately after cardiac arrest. They become less important once ROSC has been achieved. Consideration was given to the potential for pathophysiologic measures to act as surrogate assessments for longer-term functional outcomes. For example, specific neuroimaging/electrophysiologic tests might be a useful surrogate to reflect the impact of a cardiac arrest on brain function.[27] The panel considered

these outcomes may be valuable during the validation of new interventions and advancing discovery, for example, in efficacy trials. However, there was general agreement that the assessment of specific pathophysiologic manifestations as core outcomes across the wide range of effectiveness trials in this field is of limited value.

The importance of reporting adverse events was discussed at length. There was general agreement that the reporting of adverse events should occur in accordance with Good Clinical Practice guidelines, which are relevant to all clinical trials, rather than as a core outcome specific for cardiac arrest.

Although not introduced during the Delphi survey, participants discussed the importance of the quality of CPR (ie, CPR process) and its potential use as a core outcome. Such measures may include compression rate, pre-shock pause duration, compression depth, or time to intervention. There was unanimous consensus that the processes of CPR are important contributors to outcome after cardiac arrest. Participants recognized that CPR may be initiated or completed before a study intervention is applied. While CPR process may be an indicator of the quality of a resuscitation system of care or as a potential modifier of the effect of a study intervention, it was concluded that CPR process should not be a core outcome for effectiveness trials. This should not limit researchers from reporting CPR quality matrices to enable the assessment of associations between CPR performance and Core Outcome Set categories. Where such data are reported, use of standardised definitions [28] and time intervals may reduce variation in reporting.[29]

[h3]Survival

The expert panel discussed the relative importance of short-term survival, such as ROSC. The outcome was thought to be important in efficacy studies, which seek to advance discovery in this field, but contributed less toward understanding longer-term aspects of survival.

Hospital-free survival (number of days alive and permanently outside a hospital in the first 30 days after cardiac arrest) was introduced during discussions. It was recently used in a large pragmatic cardiac arrest trial[30] and offers potential statistical efficiencies over dichotomous outcomes.[31, 32] Challenges can exist around the interpretation of a composite outcome, which combines survival with length of hospital stay.

The panel concluded that longer-term survival (alive/dead) should be the core survival outcome.

[h3]Life Impact

Patient/partner participants voiced a number of potentially overlapping domains that may be affected after a cardiac arrest, which included cognition and consciousness, physical symptoms, activities of daily living, health-related quality of life (HRQoL), emotional well-being, family impact, participation, and fatigue. It was agreed that one of the most common and significant impacts of cardiac arrest are potential changes to cognition and neurologic functioning. Other contributors to daily life such as physical, social, and emotional changes after returning home were discussed and considered important. To capture these important domains of health, a multi-domain approach, including assessing an individual's HRQoL after arrest, was favored.

The panel reached consensus that neurologic function and HRQoL should be included as core outcomes.

[h3]Economic Evaluation

Although domains reflective of this core area were not prioritized by participants in the Delphi survey, the importance attributed to this core area in the OMERACT initiative suggested that further discussion of the relative importance of this core area and possible domains was required. Group discussion highlighted the complexities of capturing sufficient information to allow for a full economic analysis of costs related to cardiac arrest. While economic evaluation was judged to be important, it was agreed that there was insufficient evidence to inform categorization currently. As a result, economic measures are not being suggested as a core outcome.

[h2]Stage 4: Recommendations for Measurement Tools and Timing of Measurement

[h3]Survival

Survival to discharge and survival to 30 days were considered to be better indicators of patient recovery than shorter-term survival, such as survival to admission or 4 to 6 hours after emergency department arrival. Discussion highlighted international variation in the feasibility of collecting survival at discharge and survival at 30 days. Both time points have limitations: survival to discharge is limited by cultural differences (whether patients are discharged home to die or die predominantly in hospital) and health system differences (efficiency of discharge processes; whether long-term care is provided in hospital or home care settings). This can limit comparisons across different health systems. Survival to specific intervals (eg, 30 days)

after arrest can avoid some of these limitations, but in some settings requires consent, which, as noted elsewhere, may introduce bias through higher rates of loss to follow-up.

The writing group concluded that neither time point is perfect, and, for consistency with the Utstein recommendations,[17] it was agreed either survival to hospital discharge or survival to 30 days would be acceptable to report as core outcomes. Researchers are encouraged to report both measures if feasible, but should avoid reporting these as a composite outcome (survival to discharge or survival to 30 days) because this impairs pooling results in a meta-analysis.

[h3]Neurologic Function

Five clinician-completed measures—the Cerebral Performance Category (CPC),[33] Structured CPC (assessment by semi-structured interview),[34] CPC-Extended,[35] the Glasgow Outcome Scale–Extended (GOS-E),[36] and modified Rankin Scale (mRS)[37]—were considered. Moderate associations between the tools suggest that they measure related, but not identical, constructs.[13, 34, 38-41] The CPC was not highly endorsed because of the lack of discrimination between scores and the potential for ceiling effects and overestimation of function.[14, 42-45] The CPC-Extended was considered to show good evidence of content validity, reliability, acceptability, and feasibility, although its use in cardiac arrest survivors was limited at this time.[35] The mRS and GOS-E appear to provide improved granularity.[40, 42] The mRS has been used more extensively in cardiac arrest survivors[13, 40, 46-54] than the GOS-E[43, 55] or CPC-Extended have.[36]

The writing group reached unanimous agreement that the mRS should be the outcome measurement tool of choice for neurologic function. The mRS is a brief, clinician-completed,

ordinal hierarchical rating scale used to determine a summary score of global disability[56, 57] after a neurologic event or condition. The mRS captures impairment of physical and cognitive abilities. Questions primarily focus on limitations in basic, instrumental, and more advanced daily activities and restrictions in ability to participate in normal social roles.[57, 58] There is evidence that it can discriminate between levels of mild and moderate disability.[57] It does not, however, provide detailed information of residual impairments and is unable to differentiate between whether effects are due to neurologic or other sources of disability.[57, 59]

[h3]How to Complete (Table 2)

mRS completion is preferably measured by direct interview with the patient and any relevant caregiver—face-to-face or, optionally, by telephone.[56] Non-standardized interview administration requires approximately 5 minutes.[56] Where patients are unable to participate in interviews because of physical, language, or cognitive impairment, proxy completion—that is, completion by informants, such as family members, caregivers, or health professionals who know the patient well—may be considered. However, proxy completion without involving the patient is associated with suboptimal levels of reliability and validity.[56, 60] Although some studies suggest that indirect mRS completion from hospital records is less accurate,[61] others suggest acceptable reliability following chart review by trained health professionals.[35, 38]

Substantial inter-rater reliability of the mRS has been described,[62] although this can be improved through digital training,[62] use of a structured interview,[58, 63] or use of a Web-based tool with 9 questions (mRS-9Q) and an mRS calculator.[64] Use of trained raters as well as a structured approach to calculating the mRS score are recommended. Raters should optionally also be familiar with problems common after cardiac arrest.

[h3]Timing

The advantages and disadvantages outlined above for reporting survival status at discharge or at 30 days apply similarly to the reporting of favorable neurologic function. Additional limitations of measuring neurologic function at discharge are that the patient will not have been exposed to normal/their previous activities to allow accurate determination of the relevant mRS category. The time of discharge is also likely to be influenced by the degree and speed of recovery, with those having the greatest disabilities remaining in hospital for longer. Additional challenges imposed by assessing neurologic function at 30 days is the requirement for the research team to specifically follow up with the patient because, unlike mortality, these data are not usually tracked routinely. Incomplete follow-up risks introducing attrition bias. Whichever time-point is selected, the outcome should be reported as measured on the day of the assessment and not the best ever achieved.

The writing group accepted that there were advantages and disadvantages to both time points, and similar to our suggestion for assessing survival status, mRS score at discharge or 30 days is considered acceptable for reporting as a core outcome. Researchers may report both time points if feasible but should avoid reporting as a composite outcome (mRS score at discharge or 30 days) because this impairs pooling results in a meta-analysis.

[h3]What to report

Historically cardiac arrest trials have dichotomized neurological outcomes into favorable or unfavorable categories based on a mRS cut off of $\leq$3.[65-67] However in stroke trials a mRS of

≤1[68] or ≤ 2[69] has been used to represent the cut off between favorable and unfavorable outcomes.

To enable consistent reporting and comparisons between papers, the writing group advised that the core outcome is presented as the number and percentages of patients in each of the 6 categories rather than solely categorizing into favorable and unfavorable neurological outcome groups. This approach also provides greater granularity on clinically relevant outcomes.[70]

To facilitate the transition to mRS as the core outcome measurement tool and to support backward comparability, the writing group was also supportive of continued reporting of CPC score over the next 5 years, in addition to mRS score.

Useful information for calculating the mRS score can be found at www.modifiedrankin.com.

The COSCA writing group suggested the use of the mRS version, where category 4 (moderate severe disability) is scored when the patient is either unable to attend to own bodily needs without assistance and/or unable to walk unassisted. This better captures the level of disability for a patient with severe cognitive impairment, but still able to walk. Outcome after cardiac arrest is less influenced by locomotor problems when compared with stroke, and this version will be more sensitive to identify extensive dependency related to severe cognitive impairment in a patient still able to walk. This version is available at www.modifiedrankin.com.

- 0 = No symptoms

- 1 = No significant disability. Able to carry out all usual activities, despite some symptoms
- 2 = Slight disability. Able to look after own affairs without assistance but unable to carry out all previous activities
- 3 = Moderate disability. Requires some help but able to walk unassisted
- 4 = Moderately severe disability. Unable to attend to own bodily needs without assistance and/or unable to walk unassisted
- 5 = Severe disability. Requires constant nursing care and attention, bedridden, incontinent
- 6 = Dead

[h3]Health-Related Quality of Life

The writing group spent considerable time deliberating which tools should be used to capture HRQoL after cardiac arrest. Key considerations were the relevance or acceptability to cardiac arrest survivors, feasibility (eg, ease of use, information collection methods), the measurement properties and their previous use in the cardiac arrest patient population, and cost. The writing group prioritized 6 generic measures of HRQoL for detailed consideration: 2 multi-item profile measures (the Short-Form 36-Item Health Survey [SF-36][71] and Short Form 12-Item Health Survey [SF-12][72, 73]) and 4 preference-based, multi-attribute utility measures (the 15-dimension Quality of Life questionnaire [15-D],[74] the Health Utilities Index version 3 [HUI3],[75] and both the original and revised versions of the EuroQol [EQ-5D-3L[76] and EQ-5D-5L,[77] respectively]). All preference-based measures include both descriptive systems and a utility index, and hence, could be used in cost-utility evaluations.[78]

The group was unable to reach consensus and recommend a single tool among these measures. Patient and public partners highlighted that none of the tools comprehensively captured their experiences of the aftermath of a cardiac arrest. In online voting, the HUI3, followed by the SF-36 and EQ-5D-5L, received the most support (Table 3). The briefest measures are the EQ-5D-5L (5 items) and HUI3 (8 items); the longest is the SF-36 (v2) (36 items). While all measures are intended to be measures of health status or HRQoL, the number of items and HRQoL coverage is varied (Table 3). The HUI3 and EQ-5D-5L have a preponderance of items that relate to physical health, whereas items within the SF-36(v2) are equally distributed between physical and mental health.[78] However, only the HUI3 includes items that measure cognition, speech, and dexterity, which are concerns relevant to cardiac arrest survivors. Only the SF-36(v2) includes an assessment of fatigue.

Preference-based utility scores can be calculated for HUI3, EQ-5D-5L, and SF-36(v2) (in the form of the SF-6D[79]), supporting their use in cost-utility evaluation. The SF-36(v2) provides the most detailed profile score—that is, separate scores are calculated across the 8 health domains, providing a more detailed assessment of health status than is otherwise afforded by the 2 summary scores. More limited descriptive profile scores can also be reported for both the HUI3 and EQ-5D across their 8 and 5 attributes, respectively. Normative population data are available for all measures, supporting data interpretation, and between-group comparisons. Estimates of meaningful change have been calculated for all measures following completion by the general population and specific patient groups, further supporting data interpretation. License requests are required for all measures, but only the EQ-5D-5L is free to use.

A review of published evidence on the reliability and validity of these measures following completion by survivors of cardiac arrest demonstrated that the strongest evidence was available for the HUI3, followed by the SF-36(v2).[80] The EQ-5D-5L has not been evaluated in this population; however, evaluations in comparable populations suggest improved data quality and psychometric performance when compared with the original EQ-5D-3L.[77]

In summary, multiple measures of HRQoL, including the SF-12(v2), SF-36(v2), EQ-5D-5L, and HUI3, are acceptable for measurement of outcomes in trials enrolling patients with cardiac arrest. Each of these has strengths and weaknesses compared with other measures available. HUI3 has been applied frequently to patients with cardiac arrest and directly measures cognition. The other measures are also acceptable.

[h3]How to Complete

Although all the above HRQoL measures were developed to be self-completed, all have been successfully interview-administered in person,[39, 41] via the telephone,[13, 55, 81, 82] or both[14] in the cardiac arrest population. Postal self-completion, although possible has been only used infrequently. However, the ability to self-complete a questionnaire after a cardiac arrest can be severely impaired by cognitive impairment (which may result in an overestimation of ability),[83] fatigue, or general poor health. Although proxy ratings of non-observable constructs such as emotional well-being and cognition may underestimate limitations,[84, 85] agreement is generally greater for more physical attributes.[84, 86, 87] Cronberg et al described interview-based proxy completion of the SF-36(v2) with 8% of survivors at 6-month follow-up.[14] Where possible, proxy completion by appropriate, well-informed assessors is suggested to ensure that the views of survivors who are unable to self-report are included in trials and the results do not underestimate the impact of cardiac arrest on HRQoL.[87]

[h3]Timing

There was consensus that HRQoL should be measured after the patient's discharge from the hospital. Patient recovery often continues to 6 months and beyond. Three-quarters of patients of a working age return to work after cardiac arrest at a median interval of 4 months.[88] The optimal time points and frequency of follow-up need to be considered in the context of study resources and overall study design. If sufficient resources are available to measure post-discharge outcomes, the group recommends—as a minimum—assessment at 90 days. The group considered that this best balanced the trade-off between costs and other implications associated with longer-term follow-up with the positive effect of the value and stability of the data and is consistent with the review of primary outcomes by Becker et al.[19] However, it is recognized that health status may continue to change in the subsequent months and that capturing this change is important.[40, 88, 89] Therefore, the group agreed that HRQoL could also be assessed at 180 days and/or 1 year. However, the longer duration of follow-up would be associated with increased logistic challenges and may be influenced by factors external to surviving a cardiac arrest.

[h1]Discussion

The COSCA Writing Group identified that survival, neurologic function, and HRQoL should be reported as core outcomes in cardiac arrest effectiveness trials. Survival status should be reported at hospital discharge and / or at 30 days. Neurologic function (measured by using the mRS) should be reported at hospital discharge and / or 30 days. HRQoL should be measured by using 1 or more tools from the HUI3, SF-36(v2), or EQ-5D-5L at 90 days and at periodic intervals up to 1 year after cardiac arrest, if resources allow.

Core outcome sets are intended to enhance standardization of the outcomes, which are reported for effectiveness trials. As such, future cardiac arrest effectiveness trials should include the core outcomes identified by COSCA as part of the *a priori*–designated primary or secondary trial outcomes. The COSs are intended to be complimentary to other outcome measures relevant to the particular intervention under evaluation. The COS recommendations sit alongside, rather than replace, tools designed to enhance the quality and transparency of health research, such as the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[90] and Consolidated Standards of Reporting Trials[91] (Figure 3). Earlier phase trials will typically focus primarily on measures of efficacy, such as biomarkers, ROSC, or immediate survival, although selected core outcomes could also be considered.

Traditionally, outcome assessment of patients experiencing cardiac arrest has focused on survival rates and clinician-based assessments of outcome.[11] However, the growth in patient-centered care and recognition of the importance of seeking to understand the impact of cardiac arrest from the perspective of the survivor demand a shift in the way in which outcomes—in particular, over the longer-term—are assessed in clinical trials. The use of well-developed questionnaires, which provide an assessment of how patients feel, function, and live their lives because of their health and health care, can provide essential patient-derived information to enhance outcome reporting in clinical trials.[92] Such questionnaires or patient-reported outcome measures may be simply categorized as *generic* or *specific* (to a condition [eg, diabetes], a problem [eg, cognition], a function [eg, activities of daily life], or a population [eg, children]).

Generic measure of HRQoL, such as those short-listed in the COSCA recommendations (HUI3, SF-36(v2), EQ-5D-5L), includes multidimensional concepts (physical, social,

emotional, and mental functioning) that provide a general assessment of HRQoL of relevance to patients and the general population, facilitating between-group comparisons and ensuring that the patient perspective is captured in clinical trials. Although the generic measures supported by COSCA start to move the focus toward patient-centered outcomes, the current tools still fail to comprehensively capture the breadth of outcomes and experiences that matter most to cardiac arrest survivors.[93-95] As consequence, the impact of cardiac arrest and associated healthcare may be incompletely assessed. Although a condition-specific measure for survivors of cardiac arrest does not currently exist, measures specific to problems of relevance to cardiac arrest survivors (eg, cognition, fatigue, anxiety, social participation) are available and have been increasingly used in this population.[13, 14, 25, 26, 96-98] Even though the COSCA recommendations do not currently include guidance for 1 or more problems or function-specific measures, per good practice guidance for outcome assessment,[84, 85] where possible, we encourage their inclusion. Although not yet evaluated in the cardiac arrest population, the PROMIS initiative (Patient Reported Outcome Measures Information System http://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis) describes a range of fixed or dynamic (computer adaptive tests) self-report measures of physical, mental and social health appropriate for use with the general population and those with chronic conditions, and hence suitable for comparing the burden of illness and treatment impact. The paucity of evidence to suggest which tools are best suited highlights the need for further research in this area.

Collecting health-related quality-of-life measures as an outcome of a clinical trial can be challenging and expensive. Sometimes, such data are missing from patients with the poorest outcomes, which may result in systematic bias, which cannot be ignored.[99, 100] To maximize the quality and timeliness of quality-of-life measures and reduce the risk of systematic bias

due to missing data, standardized administration and routine screening for avoidable missing data are advised.[100-102] The approaches used and handling of missing data should be detailed in the study protocol and standard operating procedures.[99, 101]

The writing group was cognizant of the balance that needs to be struck between the requirements of collecting the core outcomes identified by the COSCA initiative at a time of constrained research resources and the need to accelerate the pace of evidence-based change in resuscitation practices. The overall efficiency of the research pathway may be improved through a better understanding of the pathophysiology and effects of therapeutic interventions from animal and laboratory studies. By establishing proof of concept with evidence from early efficacy trials, internal pilots may reduce redundancy in effectiveness trials.[103-105] Improving the efficiency of the conduct of trials[106] and making use, where possible, of registry data[107] may reduce costs and shorten the time to complete trials. The use of fixed dichotomous analysis of ordered categorical outcomes is rarely the most statistically efficient approach and usually requires a larger sample size to demonstrate efficacy than other approaches.[68] Alternative analytical approaches such as shift analysis, ordinal logistic regression, used widely in stroke research,[68, 70] require further evaluation in the cardiac arrest population. A better understanding of measurement properties of continuous outcomes, such as hospital-free survival,[31] may also aid reductions in sample size and trial costs.

[h1]Conclusion

Through a partnership between patients, partners, clinicians, and researchers and endorsed by ILCOR, consensus emerged that a core outcome set for reporting on effectiveness studies of cardiac arrest (COSCA) should include survival, neurologic function, and health-related quality of life (HRQoL). To facilitate meaningful comparisons across studies over time,

survival status and modified Rankin scale at hospital discharge and / or 30 days should be reported. HRQoL should be measured by using 1 or more tools from the HUI3, SF-36(v2), or EQ-5D-5L at 90 days and at periodic intervals up to 1 year after cardiac arrest, if resources allow.

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References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW and Turner MB; for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation*. 2016;133:e38–e360.

2. Gräsner JT, Lefering R, Koster RW, Masterson S, Böttiger BW, Herlitz J, Wnent J, Tjelmeland IB, Ortiz FR, Maurer H, Baubin M, Mols P, Hadˇzibegovic I, Ioannides M, Škulec R, Wissenberg M, Salo A, Hubert H, Nikolaou NI, Lóczi G, Svavarsdóttir H, Semeraro F, Wright PJ, Clarens C, Pijls R, Cebula G, Correia VG, Cimpoesu D, Raffay V, Trenkler S, Markota A, Stromsoe A, Burkart R, Perkins GD and Bossaert LL; for EuReCa One Collaborators. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: a prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. *Resuscitation*. 2016;105:188–95.

3. Ong ME, Shin SD, De Souza NN, Tanaka H, Nishiuchi T, Song KJ, Ko PC, Leong BS, Khunkhlai N, Naroo GY, Sarah AK, Ng YY, Li WY and Ma MH; for the PAROS Clinical Research Network. Outcomes for out-of-hospital cardiac arrests across 7 countries in Asia: the Pan Asian Resuscitation Outcomes Study (PAROS). *Resuscitation*. 2015;96:100–8.

4. Berdowski J, Berg RA, Tijssen JG and Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. *Resuscitation*. 2010;81:1479-87.

5. Perkins GD and Cooke MW. Variability in cardiac arrest survival: the NHS Ambulance Service Quality Indicators. *Emerg Med J*. 2012;29:3–5.

6. Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, Rea T, Lowe R, Brown T, Dreyer J, Davis D, Idris A and Stiell I. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA*. 2008;300:1423-31.

7. Schwartz D and Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Chronic Dis*. 1967;20:637-48.

8. Godwin M, Ruhland L, Casson I, MacDonald S, Delva D, Birtwhistle R, Lam M and Seguin R. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. *BMC Med Res Methodol*. 2003;3:28.

9. Macefield RC, Avery KN and Blazeby JM. Integration of clinical and patient-reported outcomes in surgical oncology. *Br J Surg*. 2013;100:28–37.

10. Stanley K. Design of randomized controlled trials. *Circulation*. 2007;115:1164–9.

11. Whitehead L, Perkins GD, Clarey A and Haywood KL. A systematic review of the outcomes reported in cardiac arrest clinical trials: the need for a core outcome set. *Resuscitation*. 2015;88:150-7.

12. Aufderheide TP, Pirrallo RG, Provo TA and Lurie KG. Clinical evaluation of an inspiratory impedance threshold device during standard cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest. *Crit Care Med*. 2005;33:734-40.

13. Nichol G, Guffey D, Stiell IG, Leroux B, Cheskes S, Idris A, Kudenchuk PJ, Macphee RS, Wittwer L, Rittenberger JC, Rea TD, Sheehan K, Rac VE, Raina K, Gorman K and Aufderheide T; the Resuscitation Outcomes Consortium Investigators. Post-discharge outcomes after resuscitation from out-of-hospital cardiac arrest: a ROC PRIMED substudy. *Resuscitation*. 2015;93:74–81.

14. Cronberg T, Lilja G, Horn J, Kjaergaard J, Wise MP, Pellis T, Hovdenes J, Gasche Y, Åneman A, Stammet P, Erlinge D, Friberg H, Hassager C, Kuiper M, Wanscher M, Bosch F, Cranshaw J, Kleger GR, Persson S, Undén J, Walden A, Winkel P, Wetterslev J and Nielsen N; for the TTM Trial Investigators. Neurologic function and health-related quality of life in patients following targeted temperature management at 33°C vs 36°C after out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA Neurol*. 2015;72:634–41.

15. Cummins RO, Chamberlain DA, Abramson NS, Allen M, Baskett PJ, Becker L, Bossaert L, Delooz HH, Dick WF, Eisenberg MS, Evans TR, Holmberg S, Kerber R, Mullie A, Ornato JP, Sandoe E, Skulberg A, Tunstall-Pedoe H, Swanson R and Thies WH. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style: a statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation*. 1991;84:960–75.

16. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, Cassan P, Coovadia A, D'Este K, Finn J, Halperin H, Handley A, Herlitz J, Hickey R, Idris A, Kloeck W, Larkin GL, Mancini ME, Mason P, Mears G, Monsieurs K, Montgomery W, Morley P, Nichol G, Nolan J, Okada K, Perlman J, Shuster M, Steen PA, Sterz F, Tibballs J, Timerman S, Truitt T and Zideman D. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). *Resuscitation*. 2004;63:233–49.

17. Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, Bossaert LL, Brett SJ, Chamberlain D, de Caen AR, Deakin CD, Finn JC, Grasner JT, Hazinski MF, Iwami T, Koster RW, Lim SH, Ma MH, McNally BF, Morley PT, Morrison LJ, Monsieurs KG, Montgomery W, Nichol G, Okada K, Ong ME, Travers AH and Nolan JP; for the Utstein Collaborators. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest. *Resuscitation*. 2015;96:328–340.

18. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, Conaghan PG, Bingham CO III, Brooks P, Landewé R, March L, Simon LS, Singh JA, Strand V and Tugwell P. Developing Core Outcome Measurement Sets for Clinical Trials: OMERACT Filter 2.0. *J Clin Epidemiol*. 2014;67:745–753.

19. Becker LB, Aufderheide TP, Geocadin RG, Callaway CW, Lazar RM, Donnino MW, Nadkarni VM, Abella BS, Adrie C, Berg RA, Merchant RM, O'Connor RE, Meltzer DO, Holm MB, Longstreth WT and Halperin HR; for the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Primary outcomes for resuscitation science studies: a consensus statement from the American Heart Association. *Circulation*. 2011;124:2158–77.

20. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E and Tugwell P. Developing core outcome sets for clinical trials: issues to consider. *Trials*. 2012;13:132.

21. Gargon E, Gurung B, Medley N, Altman DG, Blazeby JM, Clarke M and Williamson PR. Choosing important health outcomes for comparative effectiveness research: a systematic review. *PLoS One*. 2014;9:e99111.

22. Elliott VJ, Rodgers DL and Brett SJ. Systematic review of quality of life and other patient-centred outcomes after cardiac arrest survival. *Resuscitation*. 2011;82:247-56.

23. Trzeciak S, Jones AE, Kilgannon JH, Fuller BM, Roberts BW, Parrillo JE and Farrar JT. Outcome measures utilized in clinical trials of interventions for post-cardiac arrest syndrome: a systematic review. *Resuscitation*. 2009;80:617–23.

24. Smith JA, Flowers P and Larkin M. *Interpretative Phenomenological Analysis: Theory, Method and Research*. London, England: Sage Publications Ltd; 2009.

25. Lilja G, Nilsson G, Nielsen N, Friberg H, Hassager C, Koopmans M, Kuiper M, Martini A, Mellinghoff J, Pelosi P, Wanscher M, Wise MP, Ostman I and Cronberg T. Anxiety and depression among out-of-hospital cardiac arrest survivors. *Resuscitation*. 2015;97:68-75.

26. Tiainen M, Poutiainen E, Oksanen T, Kaukonen KM, Pettila V, Skrifvars M, Varpula T and Castren M. Functional outcome, cognition and quality of life after out-of-hospital cardiac arrest and therapeutic hypothermia: data from a randomized controlled trial. *Scand J Trauma Resusc Emerg Med*. 2015;23:12.

27. Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C, Horn J, Nolan JP, Rossetti AO and Soar J. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. *Resuscitation*. 2014;85:1779-89.

28. Kramer-Johansen J, Edelson DP, Losert H, Kohler K and Abella BS. Uniform reporting of measured quality of cardiopulmonary resuscitation (CPR). *Resuscitation*. 2007;74:406-17.

29. Talikowska M, Tohira H, Bailey P and Finn J. Cardiopulmonary resuscitation quality: Widespread variation in data intervals used for analysis. *Resuscitation*. 2016;102:25-8.

30. Nichol G, Leroux B, Wang H, Callaway CW, Sopko G, Weisfeldt M, Stiell I, Morrison LJ, Aufderheide TP, Cheskes S, Christenson J, Kudenchuk P, Vaillancourt C, Rea TD, Idris AH, Colella R, Isaacs M, Straight R, Stephens S, Richardson J, Condle J,

Schmicker RH, Egan D, May S and Investigators OJftR. Trial of continuous or interrupted chest compressions during CPR. *N Engl J Med*. 2015;373:2203–14.

31. Nichol G, Brown SP, Perkins GD, Kim F, Sterz F, Broeckel Elrod JA, Mentzelopoulos S, Lyon R, Arabi Y, Castren M, Larsen P, Valenzuela T, Graesner JT, Youngquist S, Khunkhlai N, Wang HE, Ondrej F, Sastrias JM, Barasa A and Sayre MR. What change in outcomes after cardiac arrest is necessary to change practice? Results of an international survey. *Resuscitation*. 2016;107:115-20.

32. Morton SE, Chiew YS, Pretty C, Moltchanova E, Scarrott C, Redmond D, Shaw GM and Chase JG. Effective sample size estimation for a mechanical ventilation trial through Monte-Carlo simulation: Length of mechanical ventilation and Ventilator Free Days. *Math Biosci*. 2017;284:21-31.

33. Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrrell K and Safar P. Assessment of neurological prognosis in comatose survivors of cardiac arrest. BRCT I Study Group. *Lancet*. 1994;343:1055-9.

34. Mak M, Moulaert VR, Pijls RW and Verbunt JA. Measuring outcome after cardiac arrest: construct validity of Cerebral Performance Category. *Resuscitation*. 2016;100:6-10.

35. Balouris SA, Raina KD, Rittenberger JC, Callaway CW, Rogers JC and Holm MB. Development and validation of the Cerebral Performance Categories-Extended (CPC-E). *Resuscitation*. 2015;94:98-105.

36. Wilson JT, Pettigrew LE and Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *J Neurotrauma*. 1998;15:573-85.

37. Farrell B, Godwin J, Richards S and Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry*. 1991;54:1044-54.

38. Rittenberger JC, Raina K, Holm MB, Kim YJ and Callaway CW. Association between Cerebral Performance Category, Modified Rankin Scale, and discharge disposition after cardiac arrest. *Resuscitation*. 2011;82:1036–40.

39. Raina KD, Callaway C, Rittenberger JC and Holm MB. Neurological and functional status following cardiac arrest: method and tool utility. *Resuscitation*. 2008;79:249-56.

40. Raina KD, Rittenberger JC, Holm MB and Callaway CW. Functional Outcomes: One Year after a Cardiac Arrest. *Biomed Res Int*. 2015;2015:283608.

41. Stiell IG, Nesbitt LP, Nichol G, Maloney J, Dreyer J, Beaudoin T, Blackburn J and Wells GA; the OPALS Study Group. Comparison of the Cerebral Performance Category score and the Health Utilities Index for survivors of cardiac arrest. *Ann Emerg Med*. 2009;53:241–248.

42. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammet P, Wanscher M, Wise MP, Åneman A, Al-Subaie N, Boesgaard S, Bro-Jeppesen J, Brunetti I, Bugge JF, Hingston CD, Juffermans NP, Koopmans M, Køber L, Langørgen J, Lilja G, Møller JE, Rundgren M, Rylander C, Smid O, Werer C, Winkel P and Friberg H; for the TTM Trial Investigators. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med*. 2013;369:2197–206.

43. Deasy C, Bray J, Smith K, Harriss L, Bernard S and Cameron P; for the VACAR Steering Committee. Functional outcomes and quality of life of young adults who survive out-of-hospital cardiac arrest. *Emerg Med J*. 2013;30:532–7.

44. Arrich J, Zeiner A, Sterz F, Janata A, Uray T, Richling N, Behringer W and Herkner H. Factors associated with a change in functional outcome between one month and six months after cardiac arrest: a retrospective cohort study. *Resuscitation*. 2009;80:876-80.

45. Stiell I, Nichol G, Wells G, De Maio V, Nesbitt L, Blackburn J and Spaite D; for the OPALS Study Group. Health-related quality of life is better for cardiac arrest survivors who received citizen cardiopulmonary resuscitation. *Circulation*. 2003;108:1939–44.

46. Reynolds JC, Grunau BE, Rittenberger JC, Sawyer KN, Kurz MC and Callaway CW. Association Between Duration of Resuscitation and Favorable Outcome After Out-of-Hospital Cardiac Arrest: Implications for Prolonging or Terminating Resuscitation. *Circulation*. 2016;134:2084-2094.

47. Winther-Jensen M, Kjaergaard J, Wanscher M, Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Friberg H, Gasche Y, Horn J, Hovdenes J, Kuiper M, Pellis T, Stammet P, Wise MP, Aneman A and Hassager C. No difference in mortality between men and women after out-of-hospital cardiac arrest. *Resuscitation*. 2015;96:78-84.

48. Iqbal MB, Al-Hussaini A, Rosser G, Salehi S, Phylactou M, Rajakulasingham R, Patel J, Elliott K, Mohan P, Green R, Whitbread M, Smith R and Ilsley C. Predictors of survival and favorable functional outcomes after an out-of-hospital cardiac arrest in patients systematically brought to a dedicated heart attack center (from the Harefield Cardiac Arrest Study). *Am J Cardiol*. 2015;115:730-7.

49. Maynard C, Longstreth WT Jr, Nichol G, Hallstrom A, Kudenchuk PJ, Rea T, Copass MK, Carlbom D, Deem S, Olsufka M, Cobb LA and Kim F. Effect of prehospital induction of mild hypothermia on 3-month neurological status and 1-year survival among adults with cardiac arrest: long-term follow-up of a randomized, clinical trial. *J Am Heart Assoc*. 2015;4:e001693.

50. Winther-Jensen M, Pellis T, Kuiper M, Koopmans M, Hassager C, Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Friberg H, Gasche Y, Horn J, Hovdenes J, Stammet P, Wanscher M, Wise MP, Aneman A and Kjaergaard J. Mortality and neurological outcome in

the elderly after target temperature management for out-of-hospital cardiac arrest. *Resuscitation*. 2015;91:92-8.

51. Cheskes S, Common MR, Byers AP, Zhan C, Silver A and Morrison LJ. The association between chest compression release velocity and outcomes from out-of-hospital cardiac arrest. *Resuscitation*. 2015;86:38-43.

52. Greer DM, Scripko PD, Wu O, Edlow BL, Bartscher J, Sims JR, Camargo EE, Singhal AB and Furie KL. Hippocampal magnetic resonance imaging abnormalities in cardiac arrest are associated with poor outcome. *J Stroke Cerebrovasc Dis*. 2013;22:899-905.

53. Beesems SG, Wittebrood KM, de Haan RJ and Koster RW. Cognitive function and quality of life after successful resuscitation from cardiac arrest. *Resuscitation*. 2014;85:1269-74.

54. Nielsen N, Winkel P, Cronberg T, Erlinge D, Friberg H, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammet P, Wanscher M, Wise MP, Aneman A and Wetterslev J. Detailed statistical analysis plan for the target temperature management after out-of-hospital cardiac arrest trial. *Trials*. 2013;14:300.

55. Smith K, Andrew E, Lijovic M, Nehme Z and Bernard S. Quality of life and functional outcomes 12 months after out-of-hospital cardiac arrest. *Circulation*. 2015;131:174-81.

56. Harrison JK, McArthur KS and Quinn TJ. Assessment scales in stroke: clinimetric and clinical considerations. *Clin Interv Aging*. 2013;8:201-11.

57. Banks JL and Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke*. 2007;38:1091-6.

58. Wilson JT, Hareendran A, Hendry A, Potter J, Bone I and Muir KW. Reliability of the modified Rankin Scale across multiple raters: benefits of a structured interview. *Stroke*. 2005;36:777-81.

59. Kasner SE. Clinical interpretation and use of stroke scales. *Lancet Neurol*. 2006;5:603-12.

60. McArthur K, Beagan ML, Degnan A, Howarth RC, Mitchell KA, McQuaige FB, Shannon MA, Stott DJ and Quinn TJ. Properties of proxy-derived modified Rankin Scale assessment. *Int J Stroke*. 2013;8:403-7.

61. Quinn TJ, Ray G, Atula S, Walters MR, Dawson J and Lees KR. Deriving modified Rankin scores from medical case-records. *Stroke*. 2008;39:3421-3.

62. Quinn TJ, Lees KR, Hardemark HG, Dawson J and Walters MR. Initial experience of a digital training resource for modified Rankin scale assessment in clinical trials. *Stroke*. 2007;38:2257-61.

63. Wilson JT, Hareendran A, Grant M, Baird T, Schulz UG, Muir KW and Bone I. Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin Scale. *Stroke*. 2002;33:2243-6.

64. Patel N, Rao VA, Heilman-Espinoza ER, Lai R, Quesada RA and Flint AC. Simple and reliable determination of the modified rankin scale score in neurosurgical and neurological patients: the mRS-9Q. *Neurosurgery*. 2012;71:971-5; discussion 975.

65. Stiell IG, Nichol G, Leroux BG, Rea TD, Ornato JP, Powell J, Christenson J, Callaway CW, Kudenchuk PJ, Aufderheide TP, Idris AH, Daya MR, Wang HE, Morrison LJ, Davis D, Andrusiek D, Stephens S, Cheskes S, Schmicker RH, Fowler R, Vaillancourt C, Hostler D, Zive D, Pirrallo RG, Vilke GM, Sopko G, Weisfeldt M and Investigators ROC. Early versus later rhythm analysis in patients with out-of-hospital cardiac arrest. *N Engl J Med*. 2011;365:787-97.

66. Aufderheide TP, Nichol G, Rea TD, Brown SP, Leroux BG, Pepe PE, Kudenchuk PJ, Christenson J, Daya MR, Dorian P, Callaway CW, Idris AH, Andrusiek D, Stephens SW, Hostler D, Davis DP, Dunford JV, Pirrallo RG, Stiell IG, Clement CM, Craig A, Van Ottingham L, Schmidt TA, Wang HE, Weisfeldt ML, Ornato JP, Sopko G and Resuscitation Outcomes Consortium I. A trial of an impedance threshold device in out-of-hospital cardiac arrest. *N Engl J Med*. 2011;365:798-806.

67. Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, Bossaert LL, Brett SJ, Chamberlain D, de Caen AR, Deakin CD, Finn JC, Grasner JT, Hazinski MF, Iwami T, Koster RW, Lim SH, Ma MH, McNally BF, Morley PT, Morrison LJ, Monsieurs KG, Montgomery W, Nichol G, Okada K, Ong ME, Travers AH and Nolan JP. Cardiac arrest and cardiopulmonary resuscitation outcome reports: Update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest. *Resuscitation*. 2014.

68. Bath PM, Lees KR, Schellinger PD, Altman H, Bland M, Hogg C, Howard G, Saver JL and European Stroke Organisation Outcomes Working G. Statistical analysis of the primary outcome in acute stroke trials. *Stroke*. 2012;43:1171-8.

69. Saver JL. Novel end point analytic techniques and interpreting shifts across the entire range of outcome scales in acute stroke trials. *Stroke*. 2007;38:3055-62.

70. Lees KR, Bath PM, Schellinger PD, Kerr DM, Fulton R, Hacke W, Matchar D, Sehra R, Toni D and European Stroke Organization Outcomes Working G. Contemporary outcome measures in acute stroke research: choice of primary outcome measure. *Stroke*. 2012;43:1163-70.

71. Ware JE Jr and Sherbourne CD. The MOS 36-item short-form health survey (SF-36), I: conceptual framework and item selection. *Med Care*. 1992;30:473–83.

72. Ware J Jr, Kosinski M and Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34:220–33.

73. Jenkinson C, Stewart-Brown S, Petersen S and Paice C. Assessment of the SF-36 version 2 in the United Kingdom. *J Epidemiol Community Health*. 1999;53:46-50.

74. Sintonen H. The 15D instrument of health-related quality of life: properties and applications. *Ann Med*. 2001;33:328-36.

75. Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, DePauw S, Denton M and Boyle M. Multiattribute and single-attribute utility functions for the Health Utilities Index Mark 3 system. *Med Care*. 2002;40:113–28.

76. The EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199–208.

77. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G and Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2011;20:1727-36.

78. Richardson J, Khan MA, Iezzi A and Maxwell A. Comparing and explaining differences in the magnitude, content, and sensitivity of utilities predicted by the EQ-5D, SF-6D, HUI 3, 15D, QWB, and AQoL-8D multiattribute utility instruments. *Med Decis Making*. 2015;35:276–91.

79. Brazier J, Czoski-Murray C, Roberts J, Brown M, Symonds T and Kelleher C. Estimation of a preference-based index from a condition-specific measure: the King's Health Questionnaire. *Medical decision making : an international journal of the Society for Medical Decision Making*. 2008;28:113-26.

80. Haywood K, Pearson N, Morrison L, Castren M, Lilja G and Perkins G. Assessing Health-Related Quality of Life (HRQOL) in Survivors of Cardiac Arrest: a systematic review of patient-reported outcome measures. . *Quality of Life Research*. 2017;1:In press.

81. Longstreth WT Jr, Nichol G, Van Ottingham L and Hallstrom AP. Two simple questions to assess neurologic outcomes at 3 months after out-of-hospital cardiac arrest: experience from the public access defibrillation trial. *Resuscitation*. 2010;81:530–3.

82. Andrew E, Nehme Z, Bernard S and Smith K. Comparison of health-related quality of life and functional recovery measurement tools in out-of-hospital cardiac arrest survivors. *Resuscitation*. 2016;107:57-64.

83. Pusswald G, Fertl E, Faltl M and Auff E. Neurological rehabilitation of severely disabled cardiac arrest survivors, part II: life situation of patients and families after treatment. *Resuscitation*. 2000;47:241–248.

84. Pickard AS, Johnson JA, Feeny DH, Shuaib A, Carriere KC and Nasser AM. Agreement between patient and proxy assessments of health-related quality of life after stroke using the EQ-5D and Health Utilities Index. *Stroke*. 2004;35:607-12.

85. Irwin DE, Gross HE, Stucky BD, Thissen D, DeWitt EM, Lai JS, Amtmann D, Khastou L, Varni JW and DeWalt DA. Development of six PROMIS pediatrics proxy-report item banks. *Health and quality of life outcomes*. 2012;10:22.

86. Rogers J, Ridley S, Chrispin P, Scotton H and Lloyd D. Reliability of the next of kins' estimates of critically ill patients' quality of life. *Anaesthesia*. 1997;52:1137–43.

87. Sneeuw KC, Aaronson NK, Sprangers MA, Detmar SB, Wever LD and Schornagel JH. Value of caregiver ratings in evaluating the quality of life of patients with cancer. *J Clin Oncol*. 1997;15:1206-17.

88. Kragholm K, Wissenberg M, Mortensen RN, Fonager K, Jensen SE, Rajan S, Lippert FK, Christensen EF, Hansen PA, Lang-Jensen T, Hendriksen OM, Kober L, Gislason G,

Torp-Pedersen C and Rasmussen BS. Return to Work in Out-of-Hospital Cardiac Arrest Survivors: A Nationwide Register-Based Follow-Up Study. *Circulation*. 2015;131:1682-90.

89. Larsson IM, Wallin E, Rubertsson S and Kristofferzon ML. Health-related quality of life improves during the first six months after cardiac arrest and hypothermia treatment. *Resuscitation*. 2014;85:215-20.

90. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleza-Jeric K, Laupacis A and Moher D. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586.

91. Schulz KF, Altman DG and Moher D; and the Consort Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Trials*. 2010;11:32.

92. Haywood K, Brett J, Salek S, Marlett N, Penman C, Shklarov S, Norris C, Santana MJ and Staniszewska S. Patient and public engagement in health-related quality of life and patient-reported outcomes research: what is important and why should we care? Findings from the first ISOQOL patient engagement symposium. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2015;24:1069-76.

93. Haywood KL, Brett J, Tutton E and Staniszewska S. Patient-reported outcome measures in older people with hip fracture: a systematic review of quality and acceptability. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2016;26:799–812.

94. Pietersma S, de Vries M and van den Akker-van Marle ME. Domains of quality of life: results of a three-stage Delphi consensus procedure among patients, family of patients,

clinicians, scientists and the general public. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2014;23:1543-56.

95. Kuspinar A and Mayo NE. A review of the psychometric properties of generic utility measures in multiple sclerosis. *Pharmacoeconomics*. 2014;32:759-73.

96. Moulaert VR, van Heugten CM, Winkens B, Bakx WG, de Krom MC, Gorgels TP, Wade DT and Verbunt JA. Early neurologically-focused follow-up after cardiac arrest improves quality of life at one year: A randomised controlled trial. *Int J Cardiol*. 2015;193:8-16.

97. Perkins GD, Woollard M, Cooke MW, Deakin C, Horton J, Lall R, Lamb SE, McCabe C, Quinn T, Slowther A and Gates S; and PARAMEDIC trial collaborators. Prehospital randomised assessment of a mechanical compression device in cardiac arrest (PaRAMeDIC) trial protocol. *Scand J Trauma Resusc Emerg Med*. 2010;18:58.

98. Lilja G, Nielsen N, Friberg H, Horn J, Kjaergaard J, Nilsson F, Pellis T, Wetterslev J, Wise MP, Bosch F, Bro-Jeppesen J, Brunetti I, Buratti AF, Hassager C, Hofgren C, Insorsi A, Kuiper M, Martini A, Palmer N, Rundgren M, Rylander C, van der Veen A, Wanscher M, Watkins H and Cronberg T. Cognitive function in survivors of out-of-hospital cardiac arrest after target temperature management at 33°C versus 36°C. *Circulation*. 2015;131:1340–9.

99. Fairclough DL, Peterson HF and Chang V. Why are missing quality of life data a problem in clinical trials of cancer therapy? *Stat Med*. 1998;17:667-77.

100. Bernhard J, Cella DF, Coates AS, Fallowfield L, Ganz PA, Moinpour CM, Mosconi P, Osoba D, Simes J and Hurny C. Missing quality of life data in cancer clinical trials: serious problems and challenges. *Stat Med*. 1998;17:517-32.

101. Kyte D, Reeve BB, Efficace F, Haywood K, Mercieca-Bebber R, King MT, Norquist JM, Lenderking WR, Snyder C, Ring L, Velikova G and Calvert M. International Society for Quality of Life Research commentary on the draft European Medicines Agency reflection

paper on the use of patient-reported outcome (PRO) measures in oncology studies. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2016;25:359-62.

102. Bhardwaj A, Rehman SU, Mohammed AA, Gaggin HK, Barajas L, Barajas J, Moore SA, Sullivan D and Januzzi JL. Quality of life and chronic heart failure therapy guided by natriuretic peptides: results from the ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study. *Am Heart J*. 2012;164:793.e1-799.e1.

103. Avery KN, Williamson PR, Gamble C, O'Connell Francischetto E, Metcalfe C, Davidson P, Williams H and Blazeby JM; members of the Internal Pilot Trials Workshop supported by the Hubs for Trials Methodology Research. Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. *BMJ Open*. 2017;7:e013537.

104. Bugge C, Williams B, Hagen S, Logan J, Glazener C, Pringle S and Sinclair L. A process for Decision-making after Pilot and feasibility Trials (ADePT): development following a feasibility study of a complex intervention for pelvic organ prolapse. *Trials*. 2013;14:353.

105. Luce BR, Connor JT, Broglio KR, Mullins CD, Ishak KJ, Saunders E and Davis BR; for the RE-ADAPT (REsearch in ADAptive methods for Pragmatic Trials) Investigators. Using Bayesian adaptive trial designs for comparative effectiveness research: a virtual trial execution. *Ann Intern Med*. 2016;165:431–8.

106. Treweek S, Altman DG, Bower P, Campbell M, Chalmers I, Cotton S, Craig P, Crosby D, Davidson P, Devane D, Duley L, Dunn J, Elbourne D, Farrell B, Gamble C, Gillies K, Hood K, Lang T, Littleford R, Loudon K, McDonald A, McPherson G, Nelson A, Norrie J, Ramsay C, Sandercock P, Shanahan DR, Summerskill W, Sydes M, Williamson P

and Clarke M. Making randomised trials more efficient: report of the first meeting to discuss the Trial Forge platform. *Trials*. 2015;16:261.

107. Li G, Sajobi TT, Menon BK, Korngut L, Lowerison M, James M, Wilton SB, Williamson T, Gill S, Drogos LL, Smith EE, Vohra S, Hill MD and Thabane L; for the Symposium on Registry-Based Randomized Controlled Trials in Calgary. Registry-based randomized controlled trials—what are the advantages, challenges, and areas for future research? *J Clin Epidemiol*. 2016;80:16–24.

Table 1. Themes From Patient and Partner Interviews Relating to Disruption to Normality

Theme	Examples
Survival	Closeness to death Gratitude to be alive
Impairment and impact to activities	Fatigue Breathlessness Vision Muscle weakness Pain (eg, fractured ribs) Activities of daily living/increased dependence Cognitive function
Emotional well-being	Anxiety Confidence Depression Self-esteem Personality changes Frustration
Social well-being and participation	Participation (role: job, voluntary, career) Participation (leisure: hobbies, sports) Participation (social activities) Participation (family: relationships, intimacy)
Impact on others	Increased work/care Impact to participation—hobbies, work

	Strain on relationships Worry

1

2
3
4

Table 2. Core outcomes, time-point and preferred methods for collection

Outcome	Time-point	Preferred method	Alternative method
Survival	30 days and / or discharge	Ambulance / Hospital records Death registry	
Neurological function (mRS)	30 days and / or discharge	Face to face interview by trained raters using mRS-9Q	Informant interview Telephone assessment Review of hospital records
Quality of Life	90 days	Face-to-face (proxy completion where respondents are unable to participate)	Telephone interviews Postal questionnaire

Table 3. Summary and Item Content of Short-listed Generic HRQoL Measures (n=3)

PROM **Developer** **Website** **Cost (License)** **Completion Time**	**Conceptual Focus,** **Response Options/Recall Period, Completion Format,** **Language Versions**	**HRQoL Domains (Ferrans et al, 2005)** **(Items Per Domain)**					**How to Score**
		Symptom Status **Symptoms**	**Functional Status**				**General Health Perception**
			Physical	**Cognitive**	**Psychological**	**Social/Role**	
Preferences based (2)							
Health Utilities Index 3 **(HUI3)** www.healthutilities.com **License** for use per project; minimum fee $3000 (US) [Horsman, 2003] **Completion time:** Approximately 8 minutes self-completion	Preference-based, comprehensive system for measuring health status and HRQoL and for producing utility scores. Applicable for all persons aged 5 years and older. HUI3 classification system: describes the comprehensive health state of an individual across 8 attributes of general health (6/8 items reflect physical functional status) **Response options:** Between 4 and 6 descriptive response options (ability/disability)	Pain—severity (1)	Ambulation: Ability to walk (distances) Dexterity: Ability to use hands and fingers Senses: Vision	Cognition: ability to solve day-to-day problems (1)	Emotion: happiness and interest in life (1)		2 ways of presenting the data: 1. HUI3 utility index: scored by using single- and multiattribute utility functions HUI-specific coding

Approximately 3 minutes interview completion (not reported in cardiac arrest population) **User guide:** Available once HUI3 is purchased **Country of origin:** Canada	**Recall period:** "Current" or "Usual" —"Usual" recommended for clinical studies. Choice of 1-week, 2-week, or 4-week recall available. (Horsman et al, 2003) **Completion:** Self, interview (in person; telephone), or proxy (proxy version available) supported **Language:** 16 versions, including English, Chinese, Dutch, French, German, Italian, Japanese, Portuguese, Russian, Spanish, Swedish		Senses: Hearing Speech: Ability to be understood (5)					algorithms to support calculation of single-attribute Utility Score (Index) Index range – 0.36 to 1.00, where 1.00 is perfect health, 0 is dead, and <0 is a health state worse than death Population-based norms available 2. Multiattribute descriptive

								system—"Classification system"—reflects individual item scores
EuroQol EQ-5D-5L **(EQ-5D-5L)** www.euroqol.org/home.html **License:** For use per project; free, but use must be registered on EuroQol website: www.euroqol.org/register-to-use-eq-5d.html **Completion time:** Less than 5 minutes (not reported in cardiac arrest population)	Standardized, preference-based measure of health status for use in clinical and economic appraisal EQ-5D descriptive system: 5 items across "5 domains" (2/5 reflects physical functional status) (EQ VAS: self-rated health on a 20 cm vertical visual analogue scale) **Response options:** 5-level categorical response options per item (no problems [1] to extreme problems [5]) Completion of all items will produce a 5-digit number describing the respondent's health state (but the numerals 1–5 have no inherent arithmetic properties and should not be used as a cardinal score)	Pain/discomfort (1)	Mobility Self-care (2)	–	Anxiety/depression (1)	Usual activities (including work, study, housework, and family or leisure activities) (1)	–	2 ways of presenting the data: 1. EQ-5D-5L Index value EuroQol-specific coding algorithms to support calculation of Utility Score (Index): Crosswalk value sets from EQ-5D-

User guide: Free at following link: www.euroqol.org/about-eq-5d/publications/user-guide.html **Country of origin:** Multiple	**Recall period:** Today **Completion:** Self, interview (in person, telephone), or proxy (2 proxy versions) supported: www.euroqol.org/about-eq-5d/modes-of-administration.html **Formats:** PDA, pen and paper, proxy paper, tablet, telephone, Web: www.euroqol.org/eq-5d-products/eq-5d-5l.html **Language:** >120 language versions (see www.euroqol.org)							3L support calculation of EQ-5D-5L utility score Index range – 0.59 to 1.00, where 1.00 is perfect quality of life, 0 is death, and <0 is a health state worse than death Country-specific value sets and population-based norms available Report both measure of

								central tendency and a measure of dispersion, eg, mean and SD; median and percentiles 2. EQ-5D-5L descriptive system as a health profile: reflects individual item scores. 2.1 Report as the frequency or proportion of reported problems for each level for each dimension

								2.2 Dichotomize into "No problems" (1) and "Problems" (2–5), report frequencies of reported problems
Profile measures (1)								
Short Form 36-Item Health Survey, version 2 **(SF-36v2)** https://campaign.optum.com/optum-outcomes/what-we-do/health-surveys/sf-36v2-health-survey.html	Functional health and well-being from the patient's perspective—underpinned by 8 health domains across both physical (4) and mental (4) aspects of health Total 35 items plus 1 health transition item **Response options:** Between 3- and 6-level categorical response options per item	Bodily pain (BP) (2) Vitality (VT): fatigue/tiredness (2)	Physical functioning (PF) (10) Role limitation (RP) (4)	–	Mental health (MH) (5) Role limitation (RE) (3)	Social functioning (SF) (2)	General health (GH) (5): perceived well-being	2 ways of presenting the data: 2.1 Eight-domain profile 2.2 Two component

License For use per project; minimum fee $US Survey license request: via above URL **Completion time:** Range 5 to 30 minutes (not reported in cardiac arrest population) **User guide:** Available once SF-36v2 is purchased **Country of origin:** United States	**Recall period:** Standard recall 4 weeks; acute recall 1 week **Completion:** Self, interview (in person; telephone), or proxy supported **Language:** >170 language versions: See website The IQOLA project supported the development of conceptually equivalent and culturally appropriate translations (see www.iqola.org) **Note:** utility values A preference-based utility index, the SF-6D can be calculated after completion of the SF-36 to inform economic analyses: https://www.shef.ac.uk/scharr/sections/heds/mvh/sf-6d							summary scales: PCS, MCS Scoring requires SF-36–specific algorithm. Norm-based scoring: score transformed to 0–100 (mean 50 [SD 10]) Population-based norms available

EQ VAS indicates EuroQol visual analogue scale; HRQoL, health-related quality of life; IQOLA, International Quality of Life Assessment; MCS, mental component summary; PCS, physical component summary; PROM, patient-reported outcome measure; SD, standard deviation; VAS, visual analogue scale.

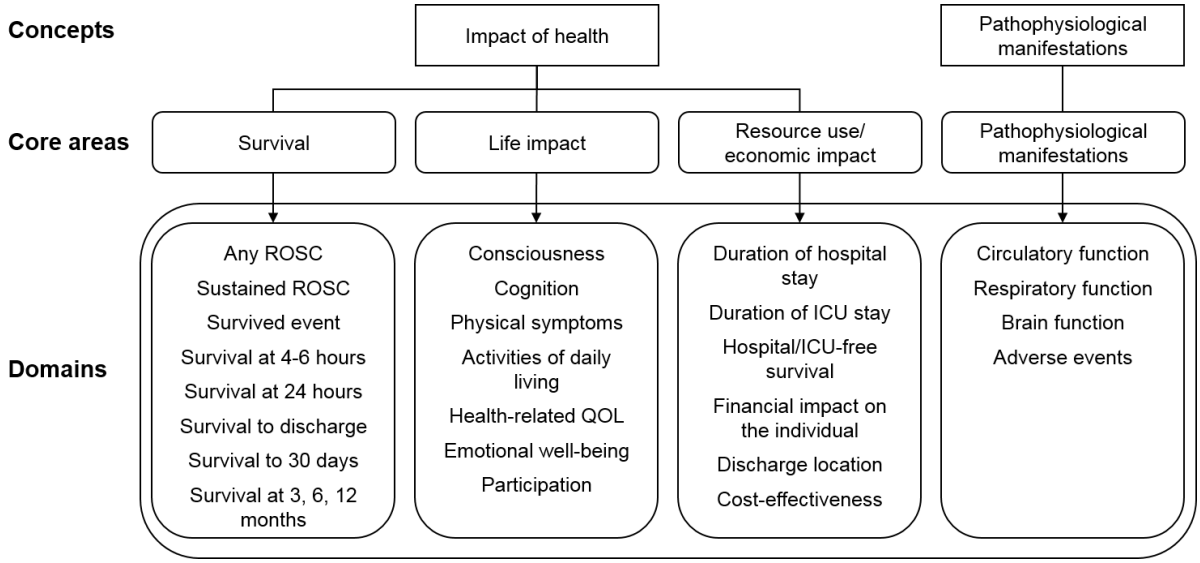

Figure 1. OMERACT framework 2.0 modified for cardiac arrest.

ICU indicates intensive care unit; QoL, quality of life; and ROSC, return of spontaneous circulation.

Core Area	**Outcome Domain**	**Timing of Measurement**				
		During CPR	*Immediately after CPR*	*During hospital stay*	*At hospital discharge*	*Within 1 year*
Pathophysiologic manifestations	Circulatory function	○	●	●▲		
	Respiratory function			▲		
	Renal function					
	Brain function (neurologic markers)		○	○▲		
	Adverse events					▲
	CPR process measures*					
Survival	Survival	●	●	●▲	●▲	●▲
Life impact	Consciousness and cognition		○	○▲	●▲	●▲
	Physical symptoms				●	●▲
	Activities of daily living				●	●▲
	Health-related quality of life				○	●▲
	Emotional well-being					▲
	Family impact					▲
	Participation				△	● ▲

	Fatigue					▲
Economic impact and resource use	Cost-effectiveness					
	Hospital-free survival*					

Figure 2: Outcome domains presented for discussion at COSCA meeting.

Symbol key: Circles indicate healthcare professionals and researchers. Triangles indicate patients and partners. Gray fill indicates strong consensus (<70%); white fill indicates moderate support. Gray boxes were not rated or ranked on their importance.

*Hospital-free survival and CPR process measures were introduced during expert panel meeting.

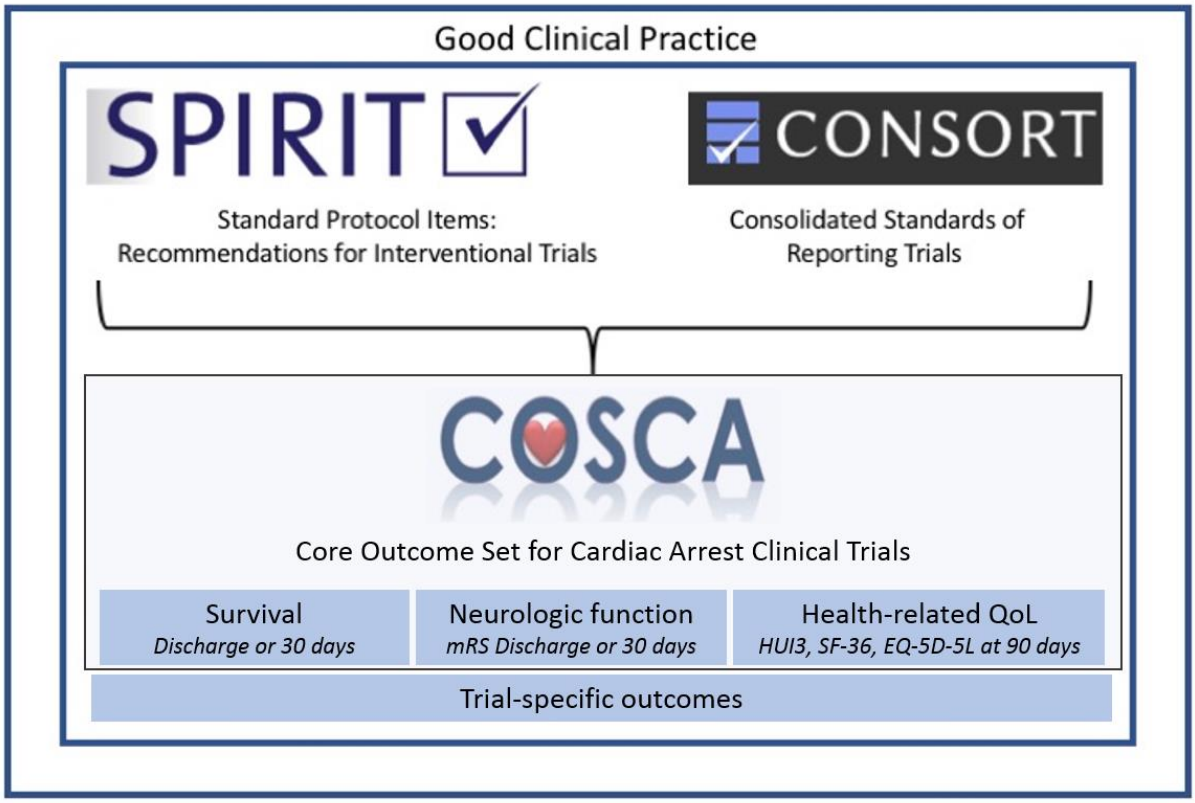

Figure 3. Clinical trials are conducted within the overall framework of good clinical practice, which supports clear and transparent reporting. Core outcome sets are suggested for inclusion as part of the *a priori*–designated primary or secondary end points of effectiveness trials. They enhance the quality and transparency of health research promoted by SPIRIT and CONSORT.

QoL indicates quality of life.